REMARKS

Before addressing the Examiner's specific rejections, Applicant provides the following general discussion regarding the claimed invention.

As discussed in the specification at page 2, lines 9-16, certain specific long circulating liposomes have been studied in human clinical trials. However, there is a significant problem with such long-circulating liposomes that results from "an inability to properly balance the enhanced circulation lifetime of the liposomes with specific drug release profiles. Thus, although investigators have successfully increased the circulation lifetimes of drugs encapsulated in pegylated liposomes, which beneficially promotes accumulation of the liposomes at tumor growth cites, they have been unable to realize acceptable drug release profiles from these liposomes for certain therapeutic agents" (please see the specification at page 2, lines 23-29).

Accordingly, what was needed was a liposomal system generally useful for improving the therapeutic index and activity of non-amphiphilic therapeutic agents (please see the specification at page 3, lines 17-19). Applicant has discovered such a system, i.e., a liposomal system that provides intermediate elimination half-lives for lipophobic therapeutic agents. These intermediate elimination half-lives are longer than the elimination half-lives of the free therapeutic agent (i.e. the agent administered in the absence of the liposomes). Thus, the liposome systems recited in the instant claims typically improve the therapeutic index and the activity of the lipophobic agents. Additionally, the drug release profiles for the liposome systems recited in the instant claims are an improvement over the insufficient drug release profiles of the previously studied long-circulating liposomes. Thus, the liposome systems recited in the instant claims solve the problem of inadequate drug release encountered in earlier long circulating liposomes (see the specification at page 2, lines 28 and 29).

Accordingly, the intermediate half-lives of the liposome systems recited in the instant claims improve the therapeutic index and the activity for the lipophobic agents – while still providing adequate release of the lipophobic agents. No prior liposome system provided this combination of properties for lipophobic therapeutic agents.

For the Examiner's convenience, the following table illustrates the ratio of components recited in various claims. These component ratios provide liposomes having beneficial intermediate elimination half-lives.

Claims	Recited components
24, 39, 44, 49, 54	HSPC:Cholesterol:DSPG in a ratio of about 4:1:0.1
25, 40, 45, 50, 55	DEPC:Cholesterol in a ratio of about 2:1
26, 41, 46, 51, 56	DEPC:Cholesterol:DSPG in a ratio of about 2:1:0.1
27, 42, 47, 52, 57	DOPC:Cholesterol in a ratio of about 2:1
28, 43, 48, 53, 58	DMPC:Cholesterol:DSPG in a ratio of about 2:1:0.1

Additionally, it is noted that each of claims 24-28 and 39-53 specifically recite "1) the elimination half-life of the therapeutic agent when administered to an animal as part of the formulation is at least as long as the elimination half-life of the therapeutic agent when administered to the same animal in the absence of the liposome, and wherein 2) the elimination half-life of the therapeutic agent when administered as part of the formulation is less than about 14 hours in a rat," which further defines an elimination half-life of intermediate duration. As discussed in greater detail below, none of the documents cited by the Examiner describe the claimed liposome systems for lipophobic therapeutic agents that provide elimination half-lives of intermediate duration.

Rejections under 35 U.S.C. § 112, second Paragraph

Claims 24-53 were rejected under 35 U.S.C. § 112, second paragraph; the Examiner stated that the claims recite two functional limitations that contradict each other. This rejection is respectfully traversed.

As an initial point, Applicant notes that claims 31-38 are not pending. Accordingly, it is believed that the rejection of these claims was an error. Applicant requests that the Examiner clarify this point if the rejection is maintained.

Claims 24-30 and 39-53 each recite the following:

> 1) the elimination half-life of the therapeutic agent when administered to an animal as part of the formulation is **at least as long** as the elimination half-life of the therapeutic agent when administered to the same animal in the absence of the liposome, and wherein 2) the elimination half-life of the therapeutic agent when administered as part of the formulation is **less than** about 14 hours in a rat. (emphasis added)

The Examiner stated that the "functional limitations 1 and 2" contradict each other in terms of half-life. It is respectfully submitted that 1 and 2 do not contradict. Phrase 1 relates to the lower end of the recited elimination half-life and phrase 2 relates to the upper end. Together, 1 and 2 establish a range (at least as long as 1, and less than 2). They do not contradict. Accordingly, the Examiner's statement is incorrect. Withdrawal of the rejection is appropriate and is requested. Additionally, it is noted that new claims 54-58 do not include the language identified by the Examiner.

Rejections under 35 U.S.C. § 103(a)

The Examiner rejected claims 24-39 [sic] and 39-53 under 35 USC § 103(a), as being unpatentable over Lopez-Berestein.

The Examiner also rejected claims 24-30 and 39-53 under 35 USC § 103(a), as being unpatentable over Hersch.

The Examiner also rejected claims 24-39 [sic] and 39-53 under 35 USC § 103(a), as being unpatentable over Lopez-Berestein in combination with Hersch.

The Examiner also rejected claims 29 and 44-48 under 35 USC § 103(a), as being unpatentable over Lopez-Berestein and Hersch individually or in combination as set forth above, further in view of Abra (5,945,122).

Applicant respectfully traverses the rejections of claim 24-30 and claims 39-53 under 35 U.S.C. § 103(a).

Hersch

Hersch describes long-circulating liposomes that do not possess the intermediate elimination half-lives recited in the instant claims. The liposomes described in Hersch have limited practical utility for use with lipophobic agents - because they will not release the

therapeutic agents in a timely manner following administration. This problem is solved by the liposome systems recited in the instant claims.

The Examiner's attention is drawn to Example 5 (Table 5) of Hersch where it is reported that the liposomes prepared therein provide a significant plasma concentration of amikacin at 14 and 24 hours after administration. Accordingly, the liposomes prepared in Hersch are long circulating liposomes, unlike the claimed liposomes.

Additionally, the Examiner's attention is drawn to Example 1 of Hersch where a lipid mixture of hydrogenated soy PC, cholesterol, and disteroyl phosphatidylglycerol in a molar ratio of 2:1:0.1 is discussed. Liposomes possessing this same ratio of lipids were prepared and evaluated in the current specification (please see the second entry in each of the tables on pages 15 and 16 of the instant specification). These lipid components produce long circulating liposomes. As discussed above, the instant claims each recite component ratios that provide liposomes having intermediate elimination half-lives. Accordingly, the liposomes of the instant claims differ significantly in composition and in properties from the materials discussed in Hersch.

Abra

Abra describes long-circulating mPEG-DSPE liposomes that do not possess the intermediate elimination half-lives of the liposomes recited in the instant claims. At column 12, lines 15-60, Abra discusses comparative stability data for the mPEG-DSPE liposomes and a comparative composition. The data in Table 2 of Abra shows that only 5% of the platinum-containing species leaked from the mPEG-DSPE liposome after 2 weeks. Like the liposomes discussed in Hersch, the liposomes discussed in Abra have limited practical utility - because they do not release the therapeutic agents in a timely manner. Accordingly, the liposomes discussed in Abra differ significantly from the liposomes recited in the instant claims in structure, stability, and drug release profile.

Lopez-Berestein

Lopez-Berestein describes liopsomes that are very different than the liposomes recited in the instant claims. Lopez-Berestein describes a liposome system where a hydrophobic therapeutic agent is trapped in the lipid bilayer of the liposome; the hydrophobic agent is not in the hydrophilic interior of the liposome. The instant claims recite a lipophobic (hydrophilic)

therapeutic agent that differs completely from the therapeutic agents that are operative in Lopez-Berestein.

CLAIM 24

Claim 24 recites:

> 24. A formulation comprising a lipophobic therapeutic agent encapsulated in a liposome that comprises **HSPC:Cholesterol:DSPG in a ratio of about 4:1:0.1**, wherein, 1) the elimination half-life of the therapeutic agent when administered to an animal as part of the formulation is at least as long as the elimination half-life of the therapeutic agent when administered to the same animal in the absence of the liposome, and wherein 2) the elimination half-life of the therapeutic agent when administered as part of the formulation is less than about 14 hours in a rat. (emphasis added)

Thus, the ratio HSPC:DSPG, as recited in claim 24, is 4:0.1 or 40:1.

In contrast, Lopez-Berestein at column 8, lines 4-7, recites:

> When the liposomes of the present invention comprises dimyristoyl phosphatidylglycerol and dimyristoyl phosphatidylcholine they are preferably in a ratio between about 1:10 and 10:1, more preferably in a ratio of about 3:7.

Hence, the liposome ratios recited in Lopez-Berestein are 10:1 and 1:10. Additionally, the specific components discussed in Lopez-Berestein (dimyristoyl phosphatidylglycerol and dimyristoyl phosphatidylcholine) differ from the HSPC and DSPG recited in claim 24.

Applicant respectfully submits that the Office action has supplied no text, reference, or knowledge explaining why one skilled in the art should equate the ratio of 10:1 or the ratio of 1:10 recited in Lopez- Berestein or any other material included in Lopez-Berestein with the recitation of claim 24, "HSPC:Cholesterol:DSPG in a ratio of about 4:1:0.1." The Office action, without citation to a reference or legal authority, recites:

> However, in the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to vary the amounts of the lipids, cholesterol and

drug from the guidance provided by Lopez-Berestein to obtain the best possible results.

Applicant respectfully submits that a combination including a ratio of about 40:1 when the art teaches a ratio of about 10:1 would not be obvious to one of ordinary skill in the art.

Also, in contrast, Hersch at column 6, lines 11-17, recites:

> The preferred ratio of HSPC:CHOL:DSPG is about 2:1:0.1 and the drug to total lipid ratio is about 1:4. Other preferred formulations include DSPG in a molar amount of 0 to 20% and most preferably in a molar amount of less than 5. Other preferred formulations include formulations where the drug to total lipid ratio is from 1:9 to 1:3.

Applicant respectfully submits that the Office action has supplied no text, reference, or knowledge explaining why one skilled in the art should equate the ratio of 2:1:0.1 recited in Hersch or any other material included in Hersch with the recitation of claim 24, "HSPC:Cholesterol:DSPG in a ratio of about 4:1:0.1."

Hence, the Office action fails to show how Lopez-Berestein or Hersch teach or suggest, **"HSPC:Cholesterol:DSPG in a ratio of about 4:1:0.1"** Thus, the Office action fails to state a *prima facie* case of obvious with respect to claim 24.

The MPEP at 706.02(j) recites:

> To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." Ex parte Clapp, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

As the Office action provides no citation to a reference that teaches or suggests a ratio of about 40:1:0.1, as recited in claim 24, Applicant concludes that the Examiner is taking "official notice." If the Office maintains the rejection, under 37 C.F.R. 1.104(d)(2), the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to

support the finding. Thus, if the Office maintains the rejection, in the next communication Applicant respectfully requests that the Examiner provide an affidavit or declaration setting forth specific factual statements and explanation to support the conclusion that that the ratio of 40:1:0.1 is obvious.

Further claim 24, recites:

> . . . the elimination half-life of the therapeutic agent when administered to an animal as part of the formulation is at least as long as the elimination half-life of the therapeutic agent when administered to the same animal in the absence of the liposome, and wherein 2) the elimination half-life of the therapeutic agent when administered as part of the formulation is less than about 14 hours in a rat . . . .

And as the Office action provides no citation to a reference that teaches or suggests the cited recitation of claim 24, Applicant concludes that the Examiner is taking "official notice." If the Office maintains the rejection, under 37 C.F.R. 1.104(d)(2), the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding. Thus, if the Office maintains the rejection, in the next communication Applicant respectfully requests that the Examiner provide an affidavit or declaration setting forth specific factual statements and explanation to support the conclusion that that the recitation of claim 24 provided above is obvious.

Therefore Applicant requests withdrawal of the rejection and reconsideration and allowance of claim 24.

CLAIMS 25, 26, 27, and 28

Claims 25, 26, 27, and 28 each recite:

> A formulation ... wherein, 1) **the elimination half-life of the therapeutic agent when administered to an animal as part of the formulation is at least as long as the elimination half-life of the therapeutic agent when administered to the same animal in the absence of the liposome, and wherein 2) the elimination half-life of the therapeutic agent when administered as part of the formulation is less than about 14 hours in a rat.** (emphasis added)

The MPEP at 706.02(j) recites:

> To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." Ex parte Clapp, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

As the Office action provides no citation to a reference that teaches or suggests, " the elimination half-life of the therapeutic agent when administered to an animal as part of the formulation is at least as long as the elimination half-life of the therapeutic agent when administered to the same animal in the absence of the liposome, and wherein 2) the elimination half-life of the therapeutic agent when administered as part of the formulation is less than about 14 hours in a rat" as recited in claims 25, 26, 27, and 28, Applicant concludes that the Examiner is taking "official notice." If the Office maintains the rejection, under 37 C.F.R. 1.104(d)(2), the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding. Thus, if the Office maintains the rejection, in the next communication Applicant respectfully requests that the Examiner provide an affidavit or declaration setting forth specific factual statements and explanation to support the conclusion that that the recitation, "the elimination half-life of the therapeutic agent when administered to an animal as part of the formulation is at least as long as the elimination half-life of the therapeutic agent when administered to the same animal in the absence of the liposome, , and wherein 2) the elimination half-life of the therapeutic agent when administered as part of the formulation is less than about 14 hours in a rat " is obvious.

Therefore Applicant requests withdrawal of the rejection and reconsideration and allowance of claims 25, 26, 27, and 28.

CLAIM 29

Claim 29, as amended, recites:

> 29. The formulation of any one of claims 24-28 wherein the therapeutic agent is cisplatin.

Claim 29 is dependent on claims 24-28. For reasons analogous to those stated above, the Office action fails to state a *prima facie* case of obviousness with respect to claim 29. Therefore applicant requests withdrawal of the rejection and reconsideration and allowance of claim 29.

Further, claim 29 is independently patentable. The Office action, at page 6 recites:

> The teachings of Lopez-Berestein and Hersch have been discussed above. What is lacking in these references is the teaching that the active is anti-neoplastic agent such as cisplatin.

Applicant agrees that neither Lopez-Berestein nor Hersch teach or suggest "cisplatin" as recited in claim 29. Further, the Office action at page 6 recites:

> Abra as pointed out before teaches liposomal encapsulation of cisplatin. It would have been obvious to one of ordinary skill in the art to encapsulate cisplatin in the liposomes of Lopez-Berestein or Hersch with a reasonable expectation of similar encapsulation since the reference of Abra shows that this compound is routinely encapsulated in liposomes for cancer treatment.

Applicant respectfully disagrees that, "It would have been obvious to one of ordinary skill in the art to encapsulate cisplatin in the liposomes of Lopez-Berestein or Hersch with a reasonable expectation of similar encapsulation since the reference of Abra shows that this compound is routinely encapsulated in liposomes for cancer treatment."

It would not have been obvious to "encapsulate cisplatin in the lipsomes" because Abra teaches away from claim 29. Abra, at col. 1, lines 63-67, recites:

> **Cisplatin, however is difficult to efficiently entrap in liposomes** because of the drug's low aqueous solubility, approximately 1,0 mg/ml at room temperature, and low lipophilicity, both of which contribute to a low drug/lipid ratio. (emphasis added)

Thus, Abra teaches "cisplatin . . . is difficult to efficiently entrap in liposomes." Hence, Abra teaches away from claim 29. Therefore, the Office action fails to state a *prima facie* case of obviousness with respect to claim 29.

Further, claim 24 (from which claim 29 depends in part) recites, "HSPC:Cholesterol: DSPG in a ratio of about 4:1:0.1." In contrast, Abra, at column 18, Example 5, recites, "the liposome composition consisted of HSPC/Chol/DSPG in a molar ratio of 50.6/44.3/5.1." This ratio of HSPC:DSPG is similar to the 10:1 (dimyristoyl phosphatidylglycerol:dimyristoyl phosphatidylcholine) ratio discussed in Lopez-Berestein, not the 40:1 ratio recited in claim 24. Thus, neither Lopez-Berestein, Hersch, nor Abra, either alone or in combination, teach or suggestion the recitaitons of claim 29.

Further, the Office action provides no citation to a reference that provides a teaching, suggestion or motivation to combine Abra with either Hersch or Lopez-Berestein or a rationale for combining Abra with either Hersch or Lopez-Berestein. Thus, Applicant concludes that the Examiner is taking "official notice." If the Office maintains the rejection, under 37 C.F.R. 1.104(d)(2), the Examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding. Thus, if the Office maintains the rejection, in the next communication Applicant respectfully requests that the Examiner provide an affidavit or declaration setting forth specific factual statements and explanation to support the conclusion that that there is a teaching, suggestion or motivation to combine the cited references.

Therefore Applicant requests withdrawal of the rejection and reconsideration and allowance of claim 29.

CLAIM 30

Claim 30 recites:

> 30. The formulation of any one of claims 24-28 wherein the therapeutic agent is amikacin or vancomycin.

Claim 30 is dependent on claims 24-38. For reasons analogous to those provided above, Applicant respectfully submits that the Office action has failed to state a *prima facie* case of obviousness with respect to claim 30 Therefore, Applicant requests withdrawal of the rejections and reconsideration and allowance of claim 30.

CLAIMS 24-30 AND 39-53

The Office action applies Hersch to the rejection of claims 24-30 and 39-53. However, Hersch teaches away from the recitations of claims 24-30 and 39-43.

Claims 24-30 and 39-43 recite, "the elimination half-life of the therapeutic agent when administered as part of the formulation is less than about 14 hours in a rat." Thus, claims 24-30 and 39-43 are directed to a liposomal system that provides intermediate elimination half-lives. In contrast, the compositions discussed by Hersch provide long-circulation times. Accordingly, the compositions of Hersch have the exact problem that is solved by the claimed compositions. Thus, Hersch, when considered alone, teaches away from claims 24-30 and 39-43. And therefore, Hersch in combination with Lopez-Berestein and Abra also teach away from claims 24-30 and 39-43. Hence, the references, by teaching away, fail to teach or suggest each of the recitations of claims 24-30 and 39-43. Thus, the Office action fails to state a *prima facie* case of obviousness with respect to claims 24-30 and 39-43. Therefore, Applicant requests withdrawal of the rejections and reconsideration and allowance of claims 24-30 and 39-53.

The Office action applies Lopez-Berestein to the rejection claims 24-30 and 39-53. However, Lopez-Berestein teaches away from the recitations of claims 24-30 and 39-43. Claims 24-30 and 39-43 each recite, "a lipophobic therapeutic agent." The specification at page 8 recites:

> The term "lipophobic therapeutic agent" includes compounds that are water soluble enough to achieve a useful level of loading by passive encapsulation and that are significantly impermeable once loaded. The term excludes agents that are both amphiphilic and that can be effectively gradient loaded into liposomes. Accordingly, the formulations of the invention are typically prepared by passive loading of liposomes.

Thus, the "lipophobic therapeutic agent," recited in the claims, is "water soluble" or hydrophilic. In contrast, Lope-Berestein, recites, "[a] lipsosomal agent for treating disseminated fungal infection in an animal, said agent comprising: (1) hamycin . . . ." However, hamycin is hydrophobic. Thus, claims 24-30 and 39-43 recite a therapeutic agent that is hydrophilic – while Lopez-Berestein teaches a therapeutic agent that is hydrophobic. Additionally, it is respectfully pointed out that the hydrophobic therapeutic agent discussed in Lopez-Berestein is embedded in the bilayer of the liposome. It is not present in the interior of the liposome. Thus, Lopez-

Berestein, when considered alone, teaches away from claims 24-30 and 39-43. Hence, the references, by teaching away, fail to teach or suggest the lipophobic therapeutic agent recited in claims 24-30 and 39-43. Thus, the Office action fails to state a *prima facie* case of obviousness with respect to claims 24-30 and claims 39-53. Therefore, Applicant requests withdrawal of the rejections and reconsideration and allowance of claims 24-30 and 39-53.

CLAIMS 24, 26, 28, 29, 30, 39, 41, 43, 44,46, 48 49, 51, AND 53

The Office action applies Lopez-Berestein to the rejection claims 24, 26, 28, 29, 30, 39, 41, 43, 44, 46, 48, 49, 51, and 53 ("recited claims"). However, Lopez-Berestein teaches away from the recitations of the rejected claims. More specifically, the rejected claims recite, "DSPG." In contrast, Lopez-Berestein discusses "DMPG" while failing to discuss "DSPG." In the liposomal systems of the rejected claims, DSPG affords colloidal stability. Further, "DSPG" with long chain C18/saturated character, is much less likely to exchange out and is better entrapped in the bilayer when compared with shorter chain DMPG. Thus, Lopez-Berestein, when considered alone, teaches away from the rejected claims. Therefore, Lopez-Berestein in combination with Hersch and Abra also teach away from the rejected claims. Hence, the references, by teaching away, fail to teach or suggest each of the recitations of the rejected claims. Thus, the Office action fails to state a *prima facie* case of obviousness with respect to the rejected claims. Therefore, Applicant requests withdrawal of the rejections and reconsideration and allowance of claims 24, 26, 28, 29, 30, 39, 41, 43, 44, 46, 48, 49, 51, and 53.

CLAIMS 39-43

Claims 39-43 are method claims. These claims recite liposome systems that are parallel to the liposome systems recited in claims 24-28. For reasons analogous to those provided above, Applicant respectfully submits that the Office action fails to state a *prima facie* case of obviousness with respect to claims 29-43. Therefore, Applicant requests withdrawal of the rejections and reconsideration and allowance of claims 39-43.

CLAIMS 44-48

Claims 44-48 are method claims directed to "administering" an "anti-cancer agent." These claims recite liposome systems that are parallel to the liposome systems recited in claims

24-28. For reasons analogous to those stated above, Applicant respectfully submits that the Office action fails to state a *prima facie* case of obviousness with respect to claims 44-48. Therefore, Applicant requests withdrawal of the rejections and reconsideration and allowance of claims 44-48.

CLAIMS 49-53

Claims 49-53 are method claims directed to "administering" an "antibiotic agent." These claims recite liposome systems that are parallel to the liposome systems recited in claims 24-28. For reasons analogous to those stated above, Applicant respectfully submits that the Office action fails to state a *prima facie* case of obviousness with respect to claims 49-53. Therefore, Applicant requests withdrawal of the rejections and reconsideration and allowance of claims 49-53.

NEW CLAIMS 54-58

New claims 54-58 recite a lipophobic therapeutic agent and the same liposome component ratios found in parallel claims 24-28. As discussed above, these component ratios provide liposomes with intermediate elimination half lives. Accordingly, the claimed liposomal systems differ from the previous long-circulating liposomes in a significant way.

CONCLUSION

In light of the above amendments and remarks, claims 24-30 and 39-58 are believed to be in condition for allowance. The Examiner is invited to contact Applicant's Representative at the below-listed telephone number if there are any questions regarding this Response or if prosecution of this application may be assisted thereby.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 50-3503. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account 50-3503.

Respectfully submitted,

Gerard M. Jensen et al.

By their Representatives,

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